Use of Dika Fat in the Formulation of Sustained Release Theophylline Tablets and Capsules

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Abstract

Sustained release theophylline tablets and capsules were prepared with dika fat, a solid vegetable oil extracted from the kernels of Irvingia gabonesis var gabonesis and var excelsia. Anhydrous theophylline was incorporated into dika fat by the fusion method. The in vitro release of the theophylline was monitored by the so-called half change dissolution method in stimulated gastric juice USP without pepsin and in stimulated intestinal juice without pancreatin, respectively. The USP XX paddle method was used. A level of sustained release was achieved over a 6-h period in both the tabletted and encapsulated dosage forms. The theophylline formulations containing dika fat, prepared in this study, exhibited dissolution profiles similar to those of Theo 24, Theodur and Respid, some commercial sustained release theophylline formulations.

Keywords: Theophylline, Dika fat matrix, Sustained release, Tablets, Capsules

Introduction

Dika fat is a solid edible vegetable oil extracted from the kernels of *Irvingia gabonesis var gabonesis* and *var excelsia*. It is a dry, free flowing non-caking powder, low in ash content and with practically no trace of heavy metals. Dika fat shows superior inertness and excellent storage stability (Onyechi, 1987**).** This fat has been evaluated as a tablet lubricant in basic lactose granulation in which it is most effective when added in the dry state in the last blending operation before compression (Udeala *et al.,* 1980).

Oral administration of drugs using controlled release formulations is a popular concept which has attracted the attention of formulation pharmacists for over five decades. This is because of the advantages such formulations have over their conventional counterparts. The advantages include: reduction of dosage frequency, constant pharmacodynamic response, patient compliance and reduction of side effects of active ingredients**.**

Most commercially available sustained release products exploit one of two simple mechanisms. These are, a reservoir limited by a diffusional barrier (Rao *et al*, 1988) and a matrix in which drug is embedded (Conti *et al*, 2007). In matrix devices, the drug is incorporated into a non-disintegrating inert matrix. Drug release in such devices is defined by a pore structure created by leaching the soluble drug, with, if necessary, soluble carriers. Theoretically the release rate is proportional to the square root of time (Korsmeyer *et al.*, 1983). Other matrix devices simply erode in the gastrointestinal tract, drug release rate declining with surface area (Karasulu *et al.*, 2000).

The purpose of this study was to evaluate the potential of Dika fat as a sustained release excipient. Theophylline was dispersed in a matrix system containing dika fat by the fusion method. The formulation mixture was either encapsulated or tabletted and evaluated for theophylline release *in vitro*. Theophylline was chosen as a model drug for this study because it possesses some of the properties of drugs best suited for sustained release formulations. These properties include short half-life, small dose, and uniform absorption in the gastro-intestinal tract and use in the treatment of chronic conditions (BNF, 2002-2003)**.** Also, theophylline has been subject of publications on sustained release (Ofoefule and Chukwu, 1998; Semde *et al.*, 2000; Saha *et al.*, 2001; Jianhong *et al.,* 2005).

Materials and Methods

Materials: Dika fat was obtained from *Irvingia gabonesis var gabonesis* and *var excelsia* by soxhlet extraction as previously described (Onyechi, 1987). The fat was further purified, bleached and deodorized (Onyechi, 1987).

The following chemicals were used as purchased from the manufacturers: lactose USP, theophylline, monobasic potassium phosphate (Merck, USA), sodium hydroxide, sodium chloride, hydrochloric acid (M&B Chemicals), magnesium stearate (BDH chemicals), Fast Flo Lactose (Foremost Diaries, USA) Slow-Bid (William Rorer Inc., USA) Theo 24 (Searle and Co., USA) and Theodur (Key Pharm., USA). RESPID (Boehringer Ingelheim, USA) tablets were also used.

Differential scanning calorimetry (DSC): Thermal analyses were performed on dika fat, theophylline and 1:1 (w/w) physical mixture of dika fat and theophylline respectively. Thermal curves were obtained using a Perkin-Elmer DSC-4 Differential Scanning Calorimeter (Perkin-Elmer Corp., Norwalk, CT, USA) equipped with a Bascom Turner Recorder and Data Acquisition system (Bascom Turner Instruments, MT, USA). After being firmly powdered, 2-8 mg samples of test substances were weighed out and encapsulated in an aluminum pan with crimp-on lids. Thermograms were obtained at a

constant heating range setting of 20 mcal per minute, in an atmosphere of nitrogen and recorded at a constant chart speed of one inch per minute. Theophylline and a 1:1 mixture of the drug and dika fat were heated over the temperature range 20 to 220^{0}C.

Preparation of theophylline granules: A 500g sample of granules was a formulated to contain 60, 20 and 20% w/w dika fat, theophylline and lactose respectively. Theophylline and lactose were added with stirring to the molten dika fat. The stirring was continued until cold when the melt solidified, thereby ensuring even distribution of the drug. The solid mass was ground and sieved through 0.595mm aperture screen. The granules were air dried overnight under room temperature of 28±1^{0}C.

Preparation of theophylline capsules: The granules prepared as described previously were manually filled into No 00 hard gelatin capsules. Each capsule contained theophylline granules equivalent to 150mg of the pure drug.

Compression of theophylline tablets: A 1:1 (w/w) mixture of Fast flo lactose and dibasic calcium phosphate was mixed with the theophylline granules prepared as previously described. This ensured the compressibility of the granules.

A batch of 500g powder mix containing theophylline granules, Fast flo lactose and dibasic calcium phosphate in 1:1:1 ratio was prepared. This was blended for 15 min in a Rotomixer (Foster Equipment Co. Ltd., Leicester, England). A 1% w/w magnesium stearate, the lubricant was then added and the blending was continued for another 5 min. The tablets were compressed in a KORSCH single punch tablet press (Type EKO, No.9228, Erweka Apparatebau GMBH, W. Germany) fitted with 9.5mm flat faced and bevelled punches. The tablet target weight was 600mg and the hardness was fixed at 5kg.

Evaluation of tablet hardness: The tablet hardness was determined on an Erweka hardness tester (Type TBH 28, No. 50675, Erweka Apparatebau GMBH, W. Germany) 24 h after the tablet had been made. The average of ten such determinations was calculated.

Dissolution studies: Theophylline release rates from the dosage forms were monitored over a 6-h period using an Erweka dissolution apparatus (Erweka Aparatebau, Type DTD, No 50288, and W. Germany). A 900ml volume of either simulated gastric juice (SGJ) USP XX without pepsin or stimulated intestinal juice (SIJ) USP XX without pancreatin respectively, maintained at 37^{0}C was used as the dissolution medium. The spindle of the dissolution apparatus was fixed to rotate at 50 rpm and the capsules were prevented from floating by the aid of a stainless steel helical spring.

The release rate of theophylline was monitored by the so-called half change dissolution method. A 500ml volume of SGJ USP without pepsin was used for the first hour, after which 250ml of this was removed and replaced by SIJ USP without pancreatic, maintained at the same temperature as the dissolution medium. The dissolution was continued for another hour after which 250ml of medium was removed and replaced. This procedure was repeated for the 6-h duration of the testing.

Analysis for the drug content of samples of the dissolution medium was performed using an SP8-400 UV/VIS spectrophotometer (Pye Unicam Ltd., Cambridge England). The absorbance of theophylline was measured at 270nm.

Percent drug dissolved was determined from the Beers law plot previously constructed using SGJ USP without pepsin and SIJ, USP without pancreatin, as media, respectively. The data was plotted as cumulative percent drug dissolved against time and each datum point represents the average of five dissolution test runs.

Results and Discussion

DSC experiments were undertaken to ascertain the compatibility of theophylline with dika fat. Fig. 1 shows the thermal curves for theophylline, dika fat and a mixture of the drug with dika fat. The transition temperature range for the melting endotherm of pure theophylline is from 270 - 280^{0}C. The average maximum peak of transition is at 274^{0}C. This transition peak corresponds to the melting of theophylline. The thermal curve for the mixture of dika fat and theophylline (Fig. 1 c) combined the features characteristic of the curves for the dika fat (Fig. 1a) and theophylline (Fig. 1b). McDaid *et al.* (2003) have stated that incompatibility is highly improbable if the thermal curve of a mixture is a simple superposition of those of the components. Incompatibility between dika and

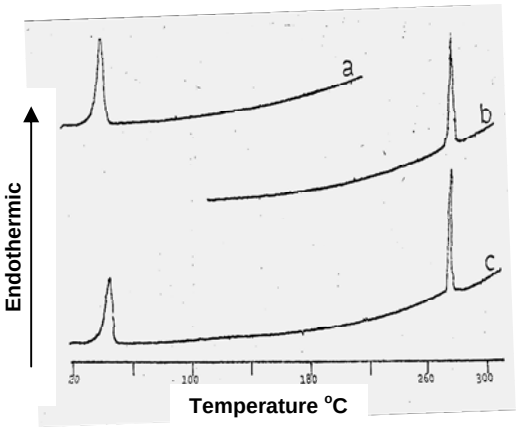

Fig. 1: DSC thermograms for a) dika fat; b) theophylline and c) 1:1 physical mixture of dika fat and theophylline

theophylline is therefore highly improbable. The release rates of theophylline from test tablets containing dika fat were determined and compared with those of commercially available dosage forms. The dissolution data is depicted in Fig. 2. Clearly there is prolonged release of theophylline from all the tablet formulations. Theoretically, sustained release products need only produce satisfactory therapeutic response with reduced frequency of administration.

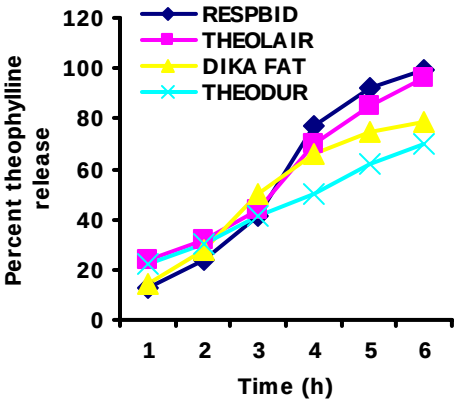

Fig. 2: Dissolution profiles of SR theophylline tablets evaluated by the half change dissolution method

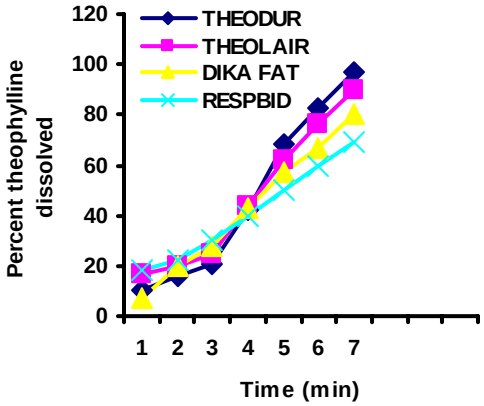

Fig. 3: The square root of time plot for the dissolution of SR theophylline tablets by the half change dissolution method

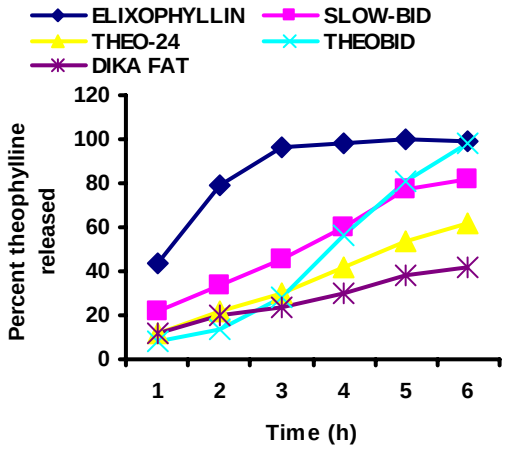

Fig. 4: Dissolution profiles of SR theophylline capsules evaluated.

Practically the release of drugs from the products should be at controlled and predictable rate. All the formulations appear to release theophylline at predictable rates. However, only the test tablets formulated with dika fat or THEODUR released the drug at near constant rates. Drug release rate in matrix devices may be proportional to the square root of time. In matrix devices and diffusion systems, where membrane permeation is the dominant mode of controlling drug release, rate of release is known to be proportional to the square root of time (Higuchi, 1963). In the case where matrix diffusion is the predominant mode of controlling drug release the rate may be constant (Higuchi, 1963). Fig. 3 shows the square root of time plot for drug release from tablets evaluated in this study. Theophylline release from the tablets, at successive time intervals, is near constant, indicating that these systems are diffusion controlled. The non-linearity at the onset and towards the end of dissolution test may be due to surface drug and finite changes in the surface area of the tablet. The latter should result in decreased theophylline release. Other factors which modify drug release in matrix systems are solubility of the drug (Brossard *et al.*, 1983; Saha *et al.*, 2001; Jambhekar *et al.*, 1987) and formulation additives (Khan and Zhu, 1999; Rohera and Parikh, 2002; Tang *et al.*, 2000).

The dissolution profiles of theophylline capsules are shown in Fig. 4. The corresponding plots of square root of time versus percent released from the same dosage forms are shown in Fig.5. Theophylline release was fastest in ELIXOPHYLLIN capsules. This was to be expected in view of the observed faster disintegration of the dosage form when compared with other encapsulated products. As with the tablet dosage forms, theophylline release were also clearly prolonged in the capsule dosage forms. The release rates though not constant appear to be predictable especially in SLOW-BID, THEO-24, THEOBID and the capsules formulated with dika fat.

Some drugs are known to exhibit pH specifity in dissolution studies either as a result of their chemistry or formulation. Drug regulatory requirements therefore recommend the testing of sustained release products at pH levels and in solutions similar to those of gastric and intestinal fluids. The effect of pH of the dissolution medium on the dissolution of theophylline from the products was evaluated. The data obtained are shown in Figs 6 and 7 which are for tablets and capsules formulated with dika fat respectively. It can be seen from both figures that theophylline release was greater in stimulated intestinal juice than in stimulated gastric juice. Theophylline dissolution from the dosage form may be dependant on whether the drug in the dosage form is the acid which is less soluble than the salt**.** The relative lower solubility of theophylline at low pH should explain the higher dissolution of the drug in the alkaline SIJ in contrast to the lower dissolution obtained in the acidic SGJ.

Conclusion: It has been shown that dika fat can be used in the formulation of sustained release theophylline dosage forms by simple fusion method. The product may be formulated either as tablets or capsules. However, such formulations should show pH specificity in drug release. The *in vivo* evaluation of theophylline released, *in vitro-in vivo* correlation of drug release from the dosage forms is being investigated.

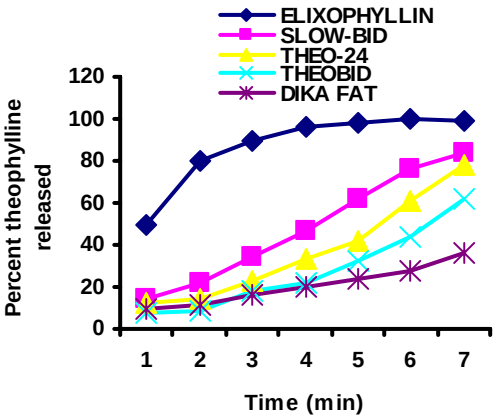

Fig. 5: The square root of time plot for the dissolution of SR theophylline capsules evaluated

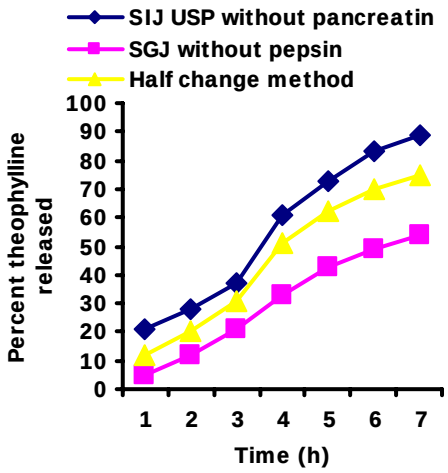

Fig. 6: Dissolution profiles of SR theophylline tablets containing dika fat

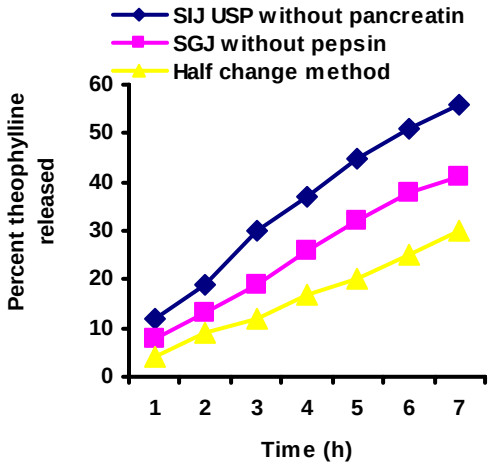

Fig. 7: Dissolution profiles of SR theophylline capsules formulated with dika fat

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